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1: Cancer Res 1996 Jan 1;56(1):100-4

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## Inhibition of the Abl protein-tyrosine kinase in vitro and in vivo by a 2-phenylaminopyrimidine derivative.

**Buchdunger E, Zimmermann J, Mett H, Meyer T, Muller M, Druker BJ, Lydon NB.**

Ciba Pharmaceuticals Division, Oncology Research Department,  
Ciba-Geigy Limited, Basel, Switzerland.

Oncogenic activation of Abl proteins due to structural modifications can occur as a result of viral transduction or chromosomal translocation. The tyrosine protein kinase activity of oncogenic Abl proteins is known to be essential for their transforming activity. Therefore, we have attempted to identify selective inhibitors of the Abl tyrosine protein kinase. Herein we describe an inhibitor (CGP 57148) of the Abl and platelet-derived growth factor (PDGF) receptor protein-tyrosine kinases from the 2-phenylaminopyrimidine class, which is highly active in vitro and in vivo. Submicromolar concentrations of the compound inhibited both v-Abl and PDGF receptor autophosphorylation and PDGF-induced c-fos mRNA expression selectively in intact cells. In contrast, ligand-induced growth factor receptor autophosphorylation in response to epidermal growth factor (EGF), insulin-like growth factor-I, and insulin showed no or weak inhibition by high concentrations of CGP 57148. c-fos mRNA expression induced by EGF, fibroblast growth factor, or phorbol ester was also insensitive to inhibition by CGP 57148. In antiproliferative assays, the compound was more than 30-100-fold more potent in inhibiting growth of v-abl-transformed PB-3c cells and v-sis-transformed BALB/c 3T3 cells relative to inhibition of EGF-dependent BALB/MK cells, interleukin-3-dependent FDC-P1 cells, and the T24 bladder carcinoma line. Furthermore, anchorage-independent growth of v-abl- and v-sis-transformed BALB/c 3T3 cells was inhibited potently by CGP 57148. When tested in vivo, CGP 57148 showed antitumor activity at tolerated doses against tumorigenic v-abl- and v-sis-transformed BALB/c 3T3 cells. In contrast, CGP 57148 had no antitumor activity when tested using src-transformed BALB/c 3T3 cells. These findings suggest that CGP 57148 may have therapeutic potential for the treatment of diseases that involve abnormal cellular proliferation induced by Abl protein-tyrosine kinase deregulation or PDGF receptor activation.

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1: Int J Obes Relat Metab Disord 2000  
Dec;24(12):1579-85

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## Pharmacokinetics of human leptin in mice and rhesus monkeys.

Ahren B, Baldwin RM, Havel PJ.

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Bo.Ahren@medforsk.mas.lu.se

**OBJECTIVE:** The pharmacokinetic characteristics of human leptin were examined in rhesus monkeys and in C57BL/6J mice fed a normal chow or a high-fat diet. **DESIGN:** For the monkey study, in nine rhesus monkeys (body weight 12.4 +/- 2.4 kg; mean +/- s.d.), recombinant met-human leptin was injected intravenously or subcutaneously (1 mg/kg). For the mouse study, after 6 months of feeding C57BL/6J mice a high-fat diet (body weight 32.9 +/- 3.6 g; n = 8) or a control diet (24.5 +/- 1.2 g; n = 6), recombinant met-human leptin was administered intraperitoneally (10 microg/g). Blood samples were collected for leptin measurement at specific time points after leptin administration. **MEASUREMENTS:** Plasma leptin concentrations were determined by radioimmunoassay and pharmacokinetic analysis was performed. **RESULTS:** Disposition of human leptin in rhesus monkeys was biphasic following intravenous administration, with a terminal phase half-life of 96.4 +/- 16.5 min and clearance of 1.8 +/- 0.2 ml/min/kg. Subcutaneously administered leptin was absorbed slowly, perhaps by a zero-order process as leptin levels appeared to plateau and remained elevated throughout the 8 h sampling period. In C57BL/6J mice, the absorption and elimination of human leptin were both first-order following intraperitoneal administration. Pharmacokinetic parameters did not differ between normal-weight mice fed a chow diet and obese mice fed a high-fat diet. The elimination half-life was 47.0 +/- 26.4 min in mice fed a high-fat diet and 49.5 +/- 12.0 min in mice fed a control diet. **CONCLUSION:** The kinetics of leptin in rhesus monkeys were biphasic and clearance was similar to values previously reported in humans. The estimated half-life was 96.4 min in rhesus monkeys and 49.5 min in normal weight mice. There was no difference in leptin kinetics between high-fat fed and control mice, suggesting that the increased baseline leptin levels in the obese mice are due to increased leptin production and secretion.

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- J Clin Endocrinol Metab. 2000 Nov;85(11):4000-2

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[com.endojournals.org](http://com.endojournals.org)**Weekly subcutaneous pegylated recombinant native human leptin (PEG-OB) administration in obese men.****Hukshorn CJ, Saris WH, Westerterp-Plantenga MS, Farid AR, Smith FJ, Campfield LA.**

Nutrition and Toxicology Research Center, NUTRIM, University of Maastricht, The Netherlands.

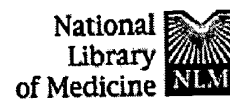
To assess the biological activity and tolerability of pegylated recombinant native human leptin (PEG-OB), 30 obese men (mean body mass index, 33.9 kg/m<sup>2</sup>) were randomized to a double-blind treatment with weekly sc injections of 20 mg PEG-OB or placebo for 12 weeks, in addition to a hypocaloric diet (deficit, 2 MJ/day). Body composition, energy expenditure, and metabolic parameters were measured before and after treatment. PEG-OB was generally well tolerated based on adverse event reports, lab values, and vital signs. Weekly sc PEG-OB led to sustained serum concentrations of PEG-OB and leptin throughout treatment. No significant differences in the delta or percent weight loss, percent body fat, sleeping metabolic rate, or respiratory quotient were observed between the PEG-OB and placebo groups. Percent change in serum triglycerides from baseline was significantly correlated with body weight loss in the PEG-OB group, but not in the placebo group. Although larger reductions in serum triglycerides were observed in the PEG-OB group compared with the placebo group, these differences were not statistically significant. We concluded that weekly injection of PEG-OB leads to sustained serum concentration of PEG-OB and leptin throughout the 12-week treatment period and is generally well tolerated. The trends observed in serum triglycerides suggest that a weekly 20-mg sc treatment with PEG-OB may have biological effects in obese men.

Publication Types:

- Clinical trial
- Multicenter study
- Randomized controlled trial

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- N Engl J Med. 2001 Apr 5;344(14):1084-6

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## Efficacy and safety of a specific inhibitor of the BCR-ABL tyrosine kinase in chronic myeloid leukemia.

Druker BJ, Talpaz M, Resta DJ, Peng B, Buchdunger E, Ford JM, Lydon NB, Kantarjian H, Capdeville R, Ohno-Jones S, Sawyers CL.

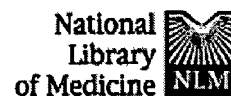
Division of Hematology and Medical Oncology, Oregon Health Sciences University, Portland 97201, USA. [drukerb@ohsu.edu](mailto:drukerb@ohsu.edu)

**BACKGROUND:** BCR-ABL is a constitutively activated tyrosine kinase that causes chronic myeloid leukemia (CML). Since tyrosine kinase activity is essential to the transforming function of BCR-ABL, an inhibitor of the kinase could be an effective treatment for CML.

**METHODS:** We conducted a phase 1, dose-escalating trial of STI571 (formerly known as CGP 57148B), a specific inhibitor of the BCR-ABL tyrosine kinase. STI571 was administered orally to 83 patients with CML in the chronic phase in whom treatment with interferon alfa had failed. Patients were successively assigned to 1 of 14 doses ranging from 25 to 1000 mg per day. **RESULTS:** Adverse effects of STI571 were minimal; the most common were nausea, myalgias, edema, and diarrhea. A maximal tolerated dose was not identified. Complete hematologic responses were observed in 53 of 54 patients treated with daily doses of 300 mg or more and typically occurred in the first four weeks of therapy. Of the 54 patients treated with doses of 300 mg or more, cytogenetic responses occurred in 29, including 17 (31 percent of the 54 patients who received this dose) with major responses (0 to 35 percent of cells in metaphase positive for the Philadelphia chromosome); 7 of these patients had complete cytogenetic remissions. **CONCLUSIONS:** STI571 is well tolerated and has significant antileukemic activity in patients with CML in whom treatment with interferon alfa had failed. Our results provide evidence of the essential role of BCR-ABL tyrosine kinase activity in CML and demonstrate the potential for the development of anticancer drugs based on the specific molecular abnormality present in a human cancer.

Publication Types:

- Clinical trial



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1: Anticancer Res 2000 Mar-Apr;20(2A):809-14

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## Growth inhibition of Ph<sup>+</sup> progenitor cells from CML patients using the tyrosine kinase inhibitor CGP57148B.

Waller CF, Ali M, Heinzinger M, Lange W.

Department of Internal Medicine I-Hematology/Oncology-,  
Albert-Ludwigs-University, Freiburg Medical Center, Germany.

**BACKGROUND:** Different methods have been investigated for their purging capacity of contaminating CML cells in autologous stem cell products. CGP57148B, a tyrphostin, has been shown to be efficient in the reduction of cell proliferation of CML cell lines and primary CML cells, as well as in the inhibition of bcr/abl-related tumor formation in animal models. **MATERIALS AND METHODS:** The effect of CGP57148B on purified CD34<sup>+</sup> progenitor cells from BM, PB, or leukapheresis products of 8 CML patients was studied under serum-free cytokine-supplemented ex vivo culture conditions. **RESULTS:** FISH as well as RT-PCR analysis showed a significant reduction of Ph<sup>+</sup> cells after 7 days ex vivo-culture in the presence of the tyrphostin. Growth of Ph<sup>-</sup> cells was almost unaffected by treatment with CGP57148B. **CONCLUSION:** Our results support the observation that CGP57148B can selectively inhibit proliferation of Ph<sup>+</sup>/bcr/abl<sup>+</sup> primary CML cells under serum-free cytokine-supplemented culture conditions.

PMID: 10810358 [PubMed - indexed for MEDLINE]

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